UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

ROCHE MOLECULAR SYSTEMS, INC.,

Plaintiff,

v.

CEPHEID,

Defendant.

Case No.14-cv-03228-EDL

ORDER GRANTING DEFENDANT'S MOTION FOR SUMMARY JUDGMENT

I. INTRODUCTION

Roche Molecular Systems, Inc. ("Roche") brought this patent infringement case against Cepheid, asserting direct and indirect infringement of U.S. Patent No. 5,643,723 (the "'723 Patent"). In its Motion for Summary Judgment, Cepheid argues that all of the asserted claims of the '723 Patent are ineligible for patent protection and the doctrine of assignor estoppel does not bar this invalidity defense because it is based on a post-assignment change in the law. After the Motion for Summary Judgment was filed, the Court granted Roche's Rule 56(d) Motion and the parties engaged in limited discovery relating to patent eligibility. Roche then filed its Opposition, arguing that Cepheid is barred by the doctrine of assignor estoppel from arguing patent ineligibility because there has been no change in law, and even if there were a change in law it would not allow Cepheid to avoid assignor estoppel and challenge the validity of the '723 Patent. Moreover, Roche argues that there is a triable issue of fact as to whether the asserted claims of the '723 Patent are invalid for lack of patent eligibility.

This Court held oral argument on the Motion for Summary Judgment on November 16, 2016. Having considered the parties' briefing as well as their presentations made during oral argument, for the following reasons, the Court concludes that assignor estoppel does not bar Cepheid's unpatentability arguments. Further, the asserted primer and method claims are directed

to non-patentable subject matter. Accordingly, Cepheid's Motion for Summary Judgment is GRANTED.

II. BACKGROUND

A. The '723 Patent

Roche alleges that Cepheid's "Xpert MTB/RIFAssay" product infringes Roche's U.S. Patent No. 5,643,723 (the "'723 Patent") entitled "Detection of a Genetic Locus Encoding Resistance to Rifampin in Microbacterial Cultures and in Clinical Specimens." See Compl. The '723 Patent relates to methods for detecting mycobacterium tuberculosis (MTB) in humans, methods for identifying MTB that is resistant to the antibiotic "rifampin," and synthetic DNA molecules called "primers" used to perform these methods. See '723 Patent at 1:13-33, 2:50-54. The '723 patent was filed in 1994, issued in 1997, and expired on July 1, 2014, shortly before Roche filed this infringement action. Compl. ¶ 6.

The '723 Patent is based on an invention by scientists working jointly at Roche and the Mayo Foundation for Medical Education and Research ("Mayo"). See Dkt. No. 49 at 4; see also Compl. Ex. 1 at 2 (cover page of '723 Patent, listing inventors). In 1994, one of the named inventors, Dr. Persing, assigned his rights in the '723 patent to his then-employer, Mayo. See Dkt. No. 49-7. Dr. Persing went on to become Executive Vice President and Chief Medical and Technology Officer at Cepheid, and is alleged to have been responsible for the overall direction of the project at Cepheid that resulted in the accused "Xpert MTB/RIFAssay" product. Rabinowitz Decl. Ex. 1. Mayo assigned its rights in the '723 Patent to Roche at the time this lawsuit was filed. See Dkt. No. 48-3.

B. General Scientific Background

1. DNA

Deoxyribonucleic acid ("DNA") consists of two chains of building blocks called "nucleotides," each having: (1) a phosphate-sugar portion that contains both a "5-prime" end and a "3-prime" end; and (2) one of four "bases" consisting of Adenine ("A"), Thymine ("T"), Cytosine ("C"), or Guanine ("G"). Marconi Decl. ¶¶ 17-18; Gottesman Decl. ¶¶ 23-24.

When a nucleotide is added to the end of a DNA chain, the 5-prime end of the incoming

nucleotide interacts with the hydroxyl group at the 3-prime end of the last nucleotide in the DNA chain through the addition of two additional phosphate residues in the incoming nucleotide, which are removed when the interaction occurs (similar to a "hook and eye" latch). This leads to the formation of a stable chemical bond, thereby incorporating the incoming nucleotide into the DNA chain. Gottesman Decl. ¶ 25. Through this process, a strand of DNA nucleotides are linked together by "phosphodiester" bonds. The first nucleotide in the strand typically has a phosphate group at its 5-prime end and the last nucleotide generally has a hydroxyl group at its 3-prime end. Unlike linear strands of plant and animal DNA, bacterial DNA takes the form of a closed circle, without 5-prime or 3-prime ends or a 3-prime hydroxyl group. Id. ¶ 26. Thus, the MTB genome is a single circular chromosome and thus does not have a 5-prime or 3-prime end, nor a 3-prime hydroxyl group in its complete, naturally occurring form. See Gottesman Decl. ¶¶ 26, 55, 84-86.

The bases of each strand of DNA form complementary base pairs such that an "A" on one strand pairs with a "T" on the other strand, and a "C" pairs with a "G" on the other strand. Marconi Decl. ¶ 19; Gottesman Decl. ¶ 29. When two strands of DNA are bound together by the attraction between complementary bases, they are said to be "hybridized." Marconi Decl. ¶ 19. Complementary base pairing means that the base sequence of one strand can be determined from its complementary strand. Marconi Decl. ¶ 19. Complementary base pairing is important in making copies of DNA in a man-made process called "polymerase chain reaction" or "PCR." Marconi Decl. ¶ 27, 30.

2. Primers and Polymerase Chain Reaction ("PCR")

PCR was a well-understood, routine and conventional technique by 1994. Marconi Decl. ¶ 25, 34; Gottesman Decl. ¶¶ 42, 48. PCR works by separating a double strand of DNA into two single strands, after which short "starter" segments of nucleic acid called "primers" bind to each separated strand to begin the copying process. Marconi Decl. ¶ 24-28; Gottesman Decl. ¶ 37-38; see also id. at 43-47. Once the primers hybridize to the separated strands, an enzyme called "polymerase" extends each primer by adding complementary nucleotides to the separated strands, resulting in two copies of the original double-stranded DNA. Marconi Decl. ¶ 29. In PCR, this process of separating double-stranded DNA into two single strands and synthesizing new

complementary strands is repeated over numerous cycles, exponentially increasing the quantity of the original DNA. Marconi Decl. ¶ 31; Gottesman Decl. ¶ 45-47. The creation of a large number of copies, known as "amplification product," makes it possible to detect whether a specific type of DNA is present. Marconi Decl. ¶ 24, 33.

In PCR, primers with nucleotides having bases that are complementary to a particular target DNA are selected so that they will hybridize to a segment of the target DNA and initiate the process of synthesizing a new complementary strand. Marconi Decl. ¶ 29-32. If the target DNA is present, the primer will hybridize to the target DNA, and PCR will result in a large amount of amplification product, which can then be detected. If the target DNA is not present, no copies will be made and no detection will occur. Marconi Decl. ¶ 33.

When a primer is paired with a template DNA strand, the primer can be extended by the addition of nucleotides to the hydroxyl group at the 3-prime end of the growing DNA strand. Gottesman Decl. ¶¶ 37-38. A free hydroxyl group at the 3-prime end of a primer or extension product is needed for DNA replication, because it provides a free end to which the next nucleotide can be attached. A segment of DNA that lacks a free hydroxyl group at the 3-prime end cannot support replication and thus cannot serve as a primer. Id. at ¶ 40.

C. MTB Testing in 1994

When the '723 Patent application was filed in 1994, the general method of MTB diagnosis was known as sputum examination by the acid-fast bacilli smear, which could identify the presence of bacterial cells but could not identify the cells as MBT. To confirm the presence of MTB, bacteria from a sample had to be grown in a culture and further tested in a process that could take weeks. Gottesman Decl. ¶ 51. The standard of care for MTB involved a regimen of antibiotics including rifampin. Gottesman Decl. ¶ 52. Outbreaks resulted because of delays in diagnosis and reporting of drug-resistant TB due to the inability to rapidly identify MTB that was resistant to rifampin and put a patient on an appropriate alternative therapy. Gottesman Decl. ¶ 53. Thus, there was a need to develop a faster procedure for identifying MTB and rifampin-resistant MTB to minimize transmission. Id. ¶ 53.

In 1994, "it was known that particular sequences in the *rpoB* gene were associated with

rifampin-resistence in MTB . . . but no test was known by which amplification of this gene could distinguish MTB from other bacteria, or indicate whether or not a biological sample contains MTB." Gottesman Decl. ¶ 58. Additionally, there was no FDA-approved nucleic acid diagnostic test for the detection of MTB until 1996, and even that test could not determine whether the MTB in the sample was rifampin-resistant. Gottesman Decl. ¶ 54, 58, Exs. 8-9; but see Gottesman Depo at 190:22-192:22 (when he made these statements, Dr. Gottesman was unaware of existing publications describing PCR-based MTB detection methods performed in a lab without FDA approval); 53-74 (discussing Puknys Decl., Exhs. C-F and acknowledging that use of PCR to detect MTB was known by 1994); 164 (acknowledging that as of 1994, articles showed tests using PCR to determine whether MTB detected was rifampin-resistant).

D. The Inventors' Discovery

The inventors of the '723 Patent discovered that a particular MTB gene (the "*rpoB* gene") contains at least eleven "position-specific signature nucleotides" that are present in MTB and not in other bacteria. Based on this discovery, the inventors devised a test using PCR that could simultaneously: (1) identify whether or not a sample contains MTB, and (2) if MTB is present, predict whether that MTB will be responsive to rifampin. Gottesman Decl. ¶ 56. This discovery represented an improvement over previously known methods for detecting MTB and predicting rifampin-resistance, as it was more accurate and faster. Gottesman Decl. ¶ 77, 79-81. While the technique of PCR was "well established" prior to 1994 (Roche Opp. at 6; Gottesman Decl. ¶ 82), PCR had not previously been performed with the particular primers identified by the inventors that could hybridize to a specific signature nucleotide for MTB. Gottesman Decl. ¶¶ 81-82.

The MTB *rpoB* gene may contain signature nucleotides in addition to the eleven identified by the inventors and claimed in the '723 Patent. Other MTB genes contain their own signature nucleotides. None of these are claimed as part of the '723 Patent. Gottesman Decl. ¶ 60.

E. The '723 Patent Claims[1]

1. The Primer Claims 17-20

The '723 Patent claims the "heretofore undiscovered presence of a set of MTB-specific signature nucleotides" present in the *rpoB* gene of MTB, which distinguishes mycobacterium tuberculosis ("MBT") from other related bacteria. '723 Patent at 2:60-3:2. Independent claim 17 recites a primer that hybridizes to the *rpoB* gene of MTB at a site that includes at least one of eleven signature nucleotides. '723 Patent at 28:16-31. Dependent claims 18-20 each add further limitations. Id. at 28:32-49. Dependent claim 20, for example, recites that the primer is selected from the group consisting of rpol05, rpo273, KY290, and KY292. Id. Because claim 20 depends on the other primer claims, claim 20 is a subset of claims 17 through 19, which encompass the primers recited in claim 20. See 35 U.S.C. § 112. All of the primers recited in claim 20 have DNA sequences that are identical to segments of the naturally occurring *rpoB* gene of MTB. Marconi Decl. ¶¶ 45, 85-88; see also Gottesman Decl. ¶ 84. Primers designed to amplify a natural segment of target DNA typically have a nucleotide sequence that is identical to a portion of the natural sequence being amplified. Marconi Decl. ¶¶ 30, 88.

2. The Method Claims 1-13

Method claims 1-13 of the '723 Patent are directed to methods for detecting MTB that include amplifying target sequences and detecting the amplification products, which, if present, indicate the presence of MTB. See '723 Patent at 25:56-27:51. Independent method claim 1 recites a method of detecting MTB that involves: (1) subjecting DNA from a sample to PCR using primers under conditions that amplify the MTB *rpoB* gene, where at least one of the primers hybridizes to one of eleven signature nucleotides; and (2) detecting whether there is amplification product (the presence of amplification product indicates that MTB is present, while the absence of amplification product indicates that MTB is not present). Id. at 25:56-27:7. Dependent claims 2-13 add limitations to claim 1 concerning PCR, PCR analysis, and primer preparation details, as well as specific primer sequences. Id. at 27:8-51; Marconi Decl. ¶¶ 57-83.

[1] This section addresses the '723 Patent claims asserted in this litigation: "method" claims 1-13 and "primer" claims 17-20. Claims 14-16 and 21-21 are not asserted in this litigation.

III. LEGAL STANDARD

A. Summary Judgment

Summary judgment shall be granted if "the pleadings, discovery and disclosure materials on file, and any affidavits show that there is no genuine issue as to any material fact and that the movant is entitled to judgment as a matter of law." Fed. R. Civ. Pro. 56(c). Material facts are those which may affect the outcome of the case. See Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 248 (1986). A dispute as to a material fact is genuine if there is sufficient evidence for a reasonable jury to return a verdict for the nonmoving party. Id. The court must view the facts in the light most favorable to the non-moving party and give it the benefit of all reasonable inferences to be drawn from those facts. Matsushita Elec. Indus. Co. v. Zenith Radio Corp., 475 U.S. 574, 587 (1986). The court must not weigh the evidence or determine the truth of the matter, but only determine whether there is a genuine issue for trial. Balint v. Carson City, 180 F.3d 1047, 1054 (9th Cir. 1999). A party seeking summary judgment bears the initial burden of informing the court of the basis for its motion, and of identifying those portions of the pleadings and discovery responses that demonstrate the absence of a genuine issue of material fact. Celotex Corp. v. Catrett, 477 U.S. 317, 323 (1986).

Where the moving party will have the burden of proof at trial, it must affirmatively demonstrate that no reasonable trier of fact could find other than for the moving party. On an issue where the nonmoving party will bear the burden of proof at trial, the moving party can prevail merely by pointing out to the district court that there is an absence of evidence to support the nonmoving party's case. Id. If the moving party meets its initial burden, the opposing party "may not rely merely on allegations or denials in its own pleading;" rather, it must set forth "specific facts showing a genuine issue for trial." See Fed. R. Civ. P. 56(e)(2); Anderson, 477 U.S. at 250. If the nonmoving party fails to show that there is a genuine issue for trial, "the moving party is entitled to judgment as a matter of law." Celotex, 477 U.S. at 323. "In ruling on a motion for summary judgment, the Court must view the evidence presented through the prism of the substantive evidentiary burden." Anderson v. Liberty Lobby, Inc., 477 U.S. 242, 254–56 (1986). Where the evidentiary burden requires "clear and convincing" evidence, "the trial judge's

summary judgment inquiry as to whether a genuine issue exists will be whether the evidence presented is such that a jury applying that evidentiary standard could reasonably find for either the plaintiff or the defendant." Id.

There is some disagreement between the parties as to whether the clear and convincing burden of proof applicable for patent invalidity also applies to patent ineligibility, or whether a "preponderance of the evidence" standard applies. See, e.g., Ultramercial, Inc. v. Hulu, LLC, 772 F.3d 709,720-21 (Fed. Cir. 2014) (Mayer, J., concurring) ("while a presumption of validity attaches in many contexts, no equivalent presumption of eligibility applies in the section 101 calculus") (citation omitted); Esoterix Genetic Labs. LLC, v. Qiagen Inc., 133 F. Supp. 3d 349, 355 (D. Mass. 2015) ("Lower courts appear to be divided on this issue," and "there is no binding precedent from the Federal Circuit"). However, even if the clear and convincing evidence standard is applicable, as discussed below there is insufficient evidence for a reasonable jury to find for Roche and therefore summary judgment is warranted regardless of the applicable standard.

B. Patent Eligibility

Section 101 of the Patent Act defines the subject matter eligible for patent protection, and provides that: "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title." 35 U.S.C. § 101. The Supreme Court "has long held that this provision contains an important implicit exception[:] Laws of nature, natural phenomena, and abstract ideas are not patentable." Ass'n for Molecular Pathology v. Myriad Genetics, Inc., -- U.S. --, 133 S.Ct. 2107, 2116 (2013) (citing Mayo Collaborative Svcs. v. Prometheus Labs., Inc., -- U.S. --, 132 S.Ct. 1289, 1293 (2012)). The Court "ha[s] interpreted § 101 and its predecessors in light of this exception for more than 150 years." Alice Corp. v. CLS Bankl Int'l., 134 S.Ct. 2347, 2354 (2914) (citing Bilski v. Kappos, 561 U.S. 593 (2010)). This is because laws of nature, natural phenomena, and abstract ideas are "the basic tools of scientific and technological work" and "monopolization of these tools through the grant of a patent might tend to impede innovation more than it would tend to promote it." Id. (citations omitted). However,

courts must "tread carefully in construing this exclusionary principle lest it swallow all of patent law." Id. (citing Mayo, 132 S.Ct. at 1293–94). "At some level, 'all inventions ... embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas.'" Id. (quoting Mayo, 132 S.Ct. at 1293–94). In applying the § 101 exception, courts must "distinguish between patents that claim the building blocks of human ingenuity and those that integrate the building blocks into something more, thereby transforming them into a patent-eligible invention." Id.

In Alice, the Supreme Court elaborated on the framework originally set forth in Mayo for "distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those claiming patent-eligible applications of those concepts." 134 S.Ct. at 2355. At step one, courts must determine "whether the claims are directed to one of those patent-ineligible concepts." Id. If so, courts must consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements transform an abstract idea into a patent-eligible invention. Id. The second step has been described as "the search for an 'inventive concept,' or some element or combination of elements sufficient to ensure that the claim in practice amounts to 'significantly more' than a patent on an ineligible concept." DDR Holdings, LLC v. Hotels.com, L.P., 773 F.3d 1245, 1255 (Fed. Cir. 2014). Though not the test itself, preemption is the concern underlying this principle. Alice, 134 S.Ct. at 2354; Bilski, 130 S.Ct. at 3218 (upholding the patent would "pre-empt use of this approach in all fields, and would effectively grant a monopoly over an abstract idea").

Patent eligibility is a threshold issue of law that may be resolved by an early dispositive motion such as this one. See, e.g., Ariosa Diagnostics, Inc. v. Sequenom, Inc.,788 F.3d 1371, 1373-75 (Fed. Cir. 2015) (affirming summary judgment of patent ineligibility for methods of detecting natural DNA). Early resolution is appropriate because "[f]ailure to recite statutory subject matter is the sort of basic deficiency, that can, and should, be exposed at the point of minimum expenditure of time and money by the parties and the court." OIP Techs., Inc. v. Amazon.com, Inc., 788 F.3d 1359, 1364 (Fed. Cir. 2015) (Mayer, J., concurring) (internal citations and quotations omitted).

IV. DISCUSSION

A. Is Cepheid Barred by the Doctrine of Assignor Estoppel From Arguing Patent Ineligibility?

As a threshold matter, Roche argues that Cepheid is barred from arguing patent ineligibility due to the doctrine of assignor estoppel. Assignor estoppel is an equitable doctrine that may be applied to prevent one who has assigned the rights to a patent (or patent application) from later contending that what was assigned is a nullity. See Diamond Scientific Co. v. Ambico, Inc., 848 F.2d 1220, 1223-25 (Fed. Cir. 1988). The basic theory of assignor estoppel is that "an assignor and parties in privity with the assignor are estopped or barred from asserting invalidity defenses." Pandrol USA, LP v. Airboss Ry. Prods., Inc., 424 F.3d 1161, 1167 (Fed. Cir. 2005). The Federal Circuit has explained that "the primary consideration in now applying the doctrine is the measure of unfairness and injustice that would be suffered by the assignee if the assignor were allowed to raise defenses of patent invalidity. Our analysis must be concerned mainly with the balance of equities between the parties." Diamond Scientific, 848 F.2d at 1225; see also Carroll Touch, Inc. v. Electro Mechanical Sys., 15 F.3d 1573, 1579 (Fed.Cir.1993) ("A determination whether assignor estoppel applies in a particular case requires a balancing of the equities between the parties."). The Federal Circuit reasoned that "it is the implicit representation by the assignor that the patent rights that he is assigning (presumably for value) are not worthless that sets the assignor apart from the rest of the world and can deprive him of the ability to challenge later the validity of the patent. To allow the assignor to make that representation at the time of the assignment (to his advantage) and later to repudiate it (again to his advantage) could work an injustice against the assignee." Diamond Scientific, 848 F.2d at 1224.

An assignor-inventor is in privity with a defendant corporation that has "availed [itself] of [the assignor-inventor's] knowledge and assistance to conduct infringement." Shamrock Techs., Inc. v. Med. Sterilization, Inc., 903 F.2d 789, 794 (Fed. Cir. 1990). For purposes of this motion, the parties do not dispute that Dr. Persing is in privity with Cepheid. See Dkt. No. 102 at 7 (Cepheid agreed in open court to assume privity for this motion). Nevertheless, Cepheid argues that it would be unfair, inequitable and contrary to the purposes of the doctrine to apply assignor

estoppel here because its ineligibility defense is based on a change in law regarding patentable subject matter that occurred long after Dr. Persing assigned his interests to May in 1994. The issues raised in this motion relating to assignor estoppel -- whether there was a post-assignment change in the law of patent eligibility and, if so, whether it impacts the application of assignor estoppel here -- are purely legal and can be decided on summary judgment.

1. A Significant Change In The Relevant Legal Landscape Occurred After Assignment.

Cepheid argues that it would be inequitable to apply assignor estoppel to bar its defense that the '723 patent contains claims that are not patent-eligible due to the Supreme Court's post-assignment ruling that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." See Ass'n for Molecular Pathology v. Myriad Genetics, Inc., -- U.S. --, 133 S. Ct. 2107, 2111 (2013). In so holding, the Court acknowledged that its decision in Myriad overturned the Patent Office's past practice of granting patents on isolated DNA sequences. See id. at 2118 (recognizin.g "the PTO's past practice of awarding gene patents"). Cepheid argues that Dr. Persing's 1994 assignment cannot reasonably prohibit him and those in privity with him, more than 20 years later after an intervening "dramatic change in law," from now arguing unpatentable subject matter. See Motion at 22 (citing Seamus Lovelace, Revisiting the Human Gene Patenting Debate in the Wake of Myriad Genetics, 42 AIPLA Q.J. 321, 322 (2014) (Myriad "represents a significant departure from the historical patent practice of the USPTO and previous Supreme Court precedent")).

Cepheid also relies on the Supreme Court's decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc. that diagnostic methods applying newly discovered natural phenomena in otherwise routine ways are not patentable. 132 S.Ct. 1289 (2012). Like Myriad, Mayo has been characterized as a relatively dramatic shift in the law of patent eligibility. For example, in Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F. 3d 1371, 1373-75 (Fed. Cir. 2015), cert. denied, No. 15-1182, 2016 U.S. LEXIS 4087 (U.S., June 27, 2016), the Federal Circuit held that certain claims relating to a genetic testing method were patent ineligible. Concurring, Judge Linn stated that the Federal Circuit's decision did not follow from an application of older case law

concerning patent ineligibility, but from "the sweeping language of the test set out" in Mayo. Id. at 1380.

Roche counters that there has been no change in the law of patent eligibility, but instead Myriad should be viewed as an "authoritative statement of what § 101 has always meant." Roche relies on Encyclopaedia Britannica, Inc. v. Dickstein Shapiro LLP, 128 F. Supp. 3d 103, 108-110 (D.D.C. 2015), aff'd, No. 15-7100, 2016 WL 3545138 (D.C. Cir. June 10, 2016), cert. denied, (U.S. Oct. 11, 2016), which stated that the "standard for patentability" as set forth in § 101 has not changed after Alice because the "Supreme Court has long held that abstract ideas are unpatentable, and has interpreted § 101 and its predecessors in light of this principle for more than 150 years" and "Alice represents the Supreme Court's definitive statement on what § 101 means -- and always meant." However, Encyclopaedia Britannica does not concern the patentability of DNA or assignor estoppel, and its holding, while correct in a formalistic sense, did not address the sea change wrought in practice in the realm of DNA patentability. Rather, it rejected a legal malpractice suit on the basis that even absent any malpractice the plaintiff would have lost its infringement action on grounds of patent ineligibility under Alice in any event. Id. at 110-16. It did not consider whether Myriad's impact on the law of DNA patentability impacts the application of assignor estoppel to assignments made long before that decision.

There can be no genuine dispute that Myriad significantly changed the legal landscape of DNA patentability. Indeed, Roche argued in an *amicus* brief to the Supreme Court during the Myriad proceedings that a ruling that isolated DNA sequences are not patent eligible would "upset reliance interests" and jeopardize patents on "DNA-based diagnostic tests." Brief for Amici Curiae Genentech, Roche Molecular Systems, et al., No. 12-398, 2013 U.S. S. Ct. Briefs LEXIS 1435, *11, *28 (March 14, 2013). During oral argument, Roche attempted to diminish the significance of its *amicus* position by arguing that when it made these statements, it was merely arguing against any sweeping decision by the Supreme Court. Nevertheless, the brief shows that Roche, like everyone else in this space, was aware of the significance of the Court's pending ruling on DNA patent law. And while Myriad may not have overruled existing Supreme Court precedent because there was no Supreme Court precedent regarding DNA patentability to

overrule, it reversed the Federal Circuit and sharply altered longstanding PTO practice and the jurisprudence of lower courts. See Myriad, 133 S.Ct. at 2118 (recognizing the PTO's "past practice of awarding gene patents"); Ass'n for Molecular Pathology v. U.S. Patent & Trademark Office, 689 F.3d 1303, 1326 (Fed. Cir. 2012), aff'd in part, rev'd in part sub nom. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013) (before reversal by the Supreme Court in Myriad, Federal Circuit held that claims to isolated DNA "are directed to patent-eligible subject matter under § 101"); USPTO Utility Examination Guidelines, 66 Fed. Reg. 1092, 1093 (Jan. 5, 2001) ("an inventor's discovery of a gene can be the basis for a patent on the genetic composition isolated from its natural state"); see also Eric J. Rogers; Can You Patent Genes? Yes and No, 93 J. Pat. & Trademark Soc'y 19 (2011) (discussing patentability of human genes and stating that "The U.S. government, particularly the Patent and Trademark Office (USPTO) and the federal courts, have continued to allow human gene patents."). This alteration in the law tips the balance of equities against application of assignor estoppel to Cepheid, a company in privity with an inventor who assigned his rights at a time when the PTO was routinely granting DNA patents, decades before the Supreme Court significantly limited the scope of such patents.

2. Myriad Tips The Balance of Equities Against Application of Assignor Estoppel.

Roche argues that, even if Myriad is viewed as a post-assignment change in the law of patent eligibility, it does not follow that Cepheid should be permitted to challenge the patentability of the '723 Patent claims despite the doctrine of assignor estoppel. The Court disagrees.

This Court has preliminarily addressed this issue in the context of a motion to stay the case pending *inter partes* reexamination by the PTAB:

> Under different circumstances, post-assignment events have been cited as precluding an assignor estoppel defense where the equities require it, and Cepheid may ultimately demonstrate that it would be inequitable to preclude it from arguing unpatentable subject matter based on Myriad due to an assignment made years earlier. See Shamrock Techs, Inc. v. Medical Sterilization, Inc., 903 F.2d 789, 795-96 (Fed. Cir. 1990) (stating that, "in a proper case general principles of equity may preclude use of assignor estoppel to bar a viable equitable defense arising from post-assignment events," but holding that the post-assignment conduct alleged -- malfeasance during PTAB appeal -- did not support an inequitable conduct

argument so assignor estoppel applied).

Dkt. No. 63 at 10. Roche argues that the so-called "Shamrock exception" identified in the Court's Order quoted above is limited to the assertion of equitable defenses based on post-assignment misconduct attributable to the assignee. See Shamrock, 903 F.2d at 795-96 ("principles of equity may preclude use of assignor estoppel to bar a viable equitable defense arising from post-assignment events").[2]

Roche contends that, as the question of patent eligibility is a legal -- rather than equitable -- defense, the equitable Shamrock exception is inapplicable and assignor estoppel should apply to bar Cepheid's defense. See In the Matter of Certain Incremental Dental Positioning Adjustment Appliances & Methods of Producing Same, Order No. 6: Initial Determination Granting Complainant's Motion for Summary Determination, USITC Inv. No. 337-TA-562, 2006 WL 1579793, at *7-8 (May 16, 2006) (holding that cases supporting position that post-assignment misconduct may bar the application of the doctrine of assignor estoppel were inapplicable to invalidity because it is a legal, rather than equitable, defense). However, Roche's reasoning that an equitable exception can never apply to a legal defense proves too much, as it would also bar application of assignor estoppel to the legal defense of patent eligibility. The case law is to the contrary, and surely Roche disagrees it should be barred from asserting assignor estoppel here. The Court has discretion to decline to apply the equitable doctrine of assignor estoppel in an appropriate case, and if a result is unfair it does not become fair merely because it arises in the context of a legal defense.

Roche also attempts to factually distinguish cases applying the Shamrock exception to hold that assignor estoppel did not bar equitable defenses. In Medical Designs v. Medical Tech., 786 F. Supp. 614, 617-18 (N.D. Tex. 1992), the court held that that it would be unfair to apply assignor estoppel to bar equitable defenses due to the post-assignment activities of an attorney who prosecuted the patents at issue, where the defendants were not profiting from the attorney's post-assignment conduct. Likewise, in Nisus Corp. v. Perma-Chink Sys. ("Nisus II"), 2005 U.S. Dist.

[2] During oral argument, Roche also argued that the Shamrock exception does not apply to one with unclean hands, but could not articulate any "unclean hands" at issue here.

LEXIS 41067, at *14-15, *20-24 (E.D. Tenn. Mar. 31, 2005), a court declined to grant summary judgment in favor of a plaintiff who argued that assignor estoppel barred the defendant's inequitable conduct defense, in part because the defense was based on post-assignment conduct.[3] Roche argues that these cases declined to apply the doctrine of assignor estoppel in light of conduct that occurred *after* a relevant assignment, whereas here Cepheid is actually relying on *pre*-assignment facts, although Roche does not make clear what pre-assignment facts it believes Cepheid is relying on. However, Cepheid's argument against assignor estoppel is not based on pre-assignment facts, but instead on a post-assignment change in law that significantly changed the legal landscape and justifies allowing a §101 challenge to the '723 Patent now.

Further, Cepheid points out that Mayo only recently assigned its rights in the '723 Patent (which it earlier acquired from Dr. Persing) to Roche. See Dkt. No. 48-3 at 6, 11.[4] At the time of Roche's recent acquisition of Dr. Persing/Mayo's rights to the '723 Patent, it knew or should have known that the asserted claims could be deemed unpatentable, as Roche had argued in its 2013 *amicus* brief in Myriad that patented DNA-based diagnostic tests would be in jeopardy if the Supreme Court ruled as it later did. It is not as if Roche paid money for a patent it thought was valuable, only to have the inventor (who had previously profited by way of an assignment) declare the patent valueless in order to profit a second time, which was the primary concern articulated as justification for assignor estoppel in Diamond Scientific.

Especially where Roche knew at the time that it acquired rights to the patent that the patent might be invalid and valueless, when considering the overarching "measure of unfairness and injustice that would be suffered by the assignee if the assignor were allowed to raise defenses of patent invalidity" and "the balance of equities between the parties," the balance of equities tips in

[3] In the same opinion, the Nisus II court summarized a prior ruling in Nisus I in which it previously held that the defendant would be estopped from asserting a patent invalidity defense based on facts or conditions in existence at the time of assignment. Id. at *9; see also Rabinowitz Decl. Ex. 2.

[4] As Roche was already the owner by assignment of the other inventors' rights in the '723 Patent, notably this recent assignment occurred just in time to allow Roche to assert an assignor estoppel defense in this case.

favor of allowing Cepheid to raise the issue of patent invalidity post-Myriad. See Diamond Scientific, 848 F.2d at 1223-25.

B. The Asserted Claims of the '723 Patent Are Ineligible for Patent Protection.

Cepheid argues that none of the asserted claims of the '723 Patent are eligible for patent protection under 35 U.S.C. § 101. Even groundbreaking discoveries can be deemed non-patentable if they arise from a newly discovered natural phenomenon combined with only routine and conventional steps. See, e.g., Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2117-20 (2013) (finding that the discovery of the location of two cancer genes did not, by itself, render them patent-eligible, noting that "[g]roundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry," but also expressly stating that the result might have been different for method claims relating to a manipulation of genes while searching for the cancer genes or a new application of knowledge about the cancer genes in question).

1. Patentability of Primer Claims 17-20

Cepheid first argues that claims 17-20 of the '723 patent are directed to unpatentable DNA primers. In Myriad, the Supreme Court held that Myriad's claims directed to "isolated BRCA1 and BRCA2" genes did not cover patent eligible subject matter because "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated." Myriad, 133 S. Ct. at 2111. The Court explained that:

> Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13.

Id. at 2116. Though Myriad had located "an important and useful gene," the Court held that "separating that gene from its surrounding genetic material is not an act of invention." Id. at 2117. Further, the Court noted that the processes used to isolate the DNA in question "were well understood, widely used, and fairly uniform insofar as any scientist engaged in the search for a gene would likely have utilized a similar approach." Id. at 2119-20. However, the Court upheld

Myriad's claims directed to non-naturally occurring cDNA versions of the genes in question because they had sequences not found in natural DNA. Id. at 2119. The Court explained that in contrast to isolating a naturally occurring gene, a "lab technician unquestionably creates something new when cDNA is made." Id.

Cepheid argues that claims 17-20 of the '723 patent are directed to primers that are structurally and functionally identical to naturally occurring DNA sequences and are thus unpatentable under Myriad and its progeny. For purposes of the Motion for Summary Judgment, there is no dispute that primers are short, single-stranded nucleic acid molecules. Marconi Decl. ¶ 26. Independent claim 17 recites a primer having 14-50 nucleotides that hybridizes to a site comprising at least one of eleven position-specific "signature nucleotides" in a region of the MTB *rpoB* gene previously known to be important for detecting antibiotic resistance in MTB. '723 Patent at 13:1-43; 28:14-31. Dependent claims 18 through 20 add limitations to claim 17, and claim 20 narrows claims 17-19 by stating that the primer is selected from a group consisting of four specified primers. '723 patent at 28:32-46; see also Table 2 (identifying sequences of these four primers); Figure 3A (locations where primers hybridize to the natural sequence of the MTB *rpoB* gene). Cepheid contends that claim 20 "indisputably encompasses primers with naturally occurring sequences" because the primers hybridize to specified regions (i.e., nucleotide sequences) of the target MTB *rpoB* gene. See '723 Patent at 5:17-18; Marconi Decl. at ¶¶ 45, 88 (typical primer designed to amplify a natural segment of DNA, such as the *rpoB* gene, has nucleotide sequence identical to a portion of the natural sequence being amplified). Because claim 20 depends from broader claims 17-19, Cepheid reasons that it is necessarily encompassed within those claims and therefore the primers in claims 17-20 all have sequences identical to those that exist in nature and cannot be patented.

Roche does not dispute Cepheid's description of the interplay between the primer claims, or that the sequences are identical (see Gottesman Decl. ¶ 84), but argues that the claimed primers differ *structurally* from naturally-occurring DNA and are thus directed to patentable subject matter. With respect to structure, both parties rely on In re BRCA1- and BRCA2- Based Hereditary Cancer Test Patent Litigation, 774 F.3d 755 (Fed. Cir. 2014). In In re BRCA1-, the

Federal Circuit examined the patentability of claims directed to "[a] pair of single-stranded DNA primers for determination of a nucleotide sequence of a BRCA1 gene by a polymerase chain reaction, the sequence of said primers being derived from human chromosome 17q, wherein the use of said primers in a polymerase chain reaction results in the synthesis of DNA having all or part of the sequence of the BRCA1 gene." Id. at 759. The Federal Circuit applied Myriad to hold that the claimed primers were "not distinguishable from the isolated DNA found patent-ineligible in Myriad and are not similar to the cDNA found to be patent-eligible. Primers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind. They are structurally identical to the ends of DNA strands found in nature." Id. at 760 (emphasis added). The Federal Circuit stated that "it makes no difference that the identified gene sequences are synthetically replicated" because they are structurally identical to naturally occurring compositions. Id.

The Federal Circuit held that it did not matter that "primers are in fact not naturally occurring because single-stranded DNA cannot be found in the human body" because separating DNA from surrounding genetic material is not alone an act of invention. Id. The Federal Circuit also rejected an argument that

> the [nucleotide] sequences, when extracted as primers, have a fundamentally different function than when they are part of a DNA strand." Id. at 760-61. The Court reasoned that "the naturally occurring genetic sequences at issue here do not perform a significantly new function. Rather, the naturally occurring material is used to form the first step in a chain reaction—a function that is performed because the primer maintains the exact same nucleotide sequence as the relevant portion of the naturally occurring sequence. One of the primary functions of DNA's structure in nature is that complementary nucleotide sequences bind to each other. It is this same function that is exploited here—the primer binds to its complementary nucleotide sequence. Thus, just as in nature, primers utilize the innate ability of DNA to bind to itself."

Id. at 761. The Federal Circuit concluded that:

> We do not read the Supreme Court's opinion in Myriad as conferring patent eligibility on composition of matter claims directed to naturally occurring DNA strands under such circumstances. A DNA structure with a function similar to that found in nature can only be patent eligible as a composition of matter if it has a unique structure, different from anything found in nature. Myriad, 133 S.Ct. at 2116–17 (citing Chakrabarty, 447 U.S.

> at 309–10, 100 S.Ct. 2204). Primers do not have such a different structure and are patent ineligible.

Id.

Cepheid argues that just as in In re BRCA1-, here it is undisputed that the claimed primers have sequences that are identical to naturally occurring DNA strands and do not perform a significantly new function, so they are not eligible for patent protection. Roche counters that, though they may have the same sequences, the primers claimed in the '723 Patent are structurally and chemically distinct from naturally occurring DNA, and are thus distinguishable from the isolated DNA coding defined exclusively by its genetic sequence found patent-ineligible in Myriad and the primers at issue in In Re BRCA1-. Roche focuses on the Supreme Court's conclusion in Myriad that severing chemical bonds to isolate DNA was insufficient because "Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA," while DNA claims directed to non-naturally occurring cDNA created by a lab technician were patentable. Myriad, 133 S.Ct. at 2118-19. Roche argues that here, its primer claims *are* expressed in terms of chemical composition and *do* rely on chemical changes resulting from isolating sections of DNA and are not identical to DNA.

Specifically, Roche argues that its claimed primers must have both a 3-prime end and a 3-hydroxyl group (which provides a free end to which the next nucleotide can be attached and is necessary for all primers), whereas the complete, naturally occurring bacterial MTB DNA molecule is circular and contains neither of these. See Gottesman Decl. ¶¶ 48, 84-86, Fig. 10. Roche argues that In re BRCA1- is distinguishable because the primers at issue there had the sequence of human DNA, which is linear and has a 3-prime end and 3-prime hydroxyl group, so the primers and the DNA were structurally identical. In contrast, the claimed primers here have a sequence of bacterial DNA which is circular and lacks a 3-prime end and 3-prime hydroxyl group (see Gottesman Decl. ¶ 27, 55, Fig. 10; Marconi Depo. at 70). Thus, according to Roche, the claimed primers differ structurally from the DNA on which they are based.

a. 3-Prime End

Dr. Gottesman testified about a way to determine which is the 3-prime and 5-prime end of

the *rpoB* gene contained within the MTB chromosome, indicating that the naturally-occurring gene does have what can be viewed as a 3-prime end. See Gottesman Depo. at 87, 89, 95. Dr. Gottesman further testified that the end of a gene sequence is different from the end of a DNA strand, and on re-direct clarified that: "DNA can have a three prime end. A gene sequence does not have an end in terms of a physical end of a DNA molecule, it has an end of the sequence but not the end of a DNA molecule." Gottesman Depo. at 187. Thus, Dr. Gottesman stated that "it is not possible to add a nucleotide to the end of a gene sequence which is part of a DNA sequence that continues past the gene sequence" because "it's not the end of the DNA with a three-prime hydroxyl." Id. at 187-88.

Roche argues that Cepheid questioned Dr. Gottesman about the 3-prime end of a gene sequence, not the physical end of a DNA strand, which is required by the claimed primers. The crux of Roche's position appears to be as follows: while an isolated gene sequence might be viewed as having a 3-prime end, in its natural form the *rpoB* gene does not have ends because it is part of a larger, circular bacterial MTB DNA molecule which does not have ends, and no nucleotide can be added to the end of this gene as it naturally occurs, so it differs structurally from the corresponding claimed primers which do have 3-prime ends and to which nucleotides can be added. Accordingly, Roche argues that there is at least a triable issue of fact as to whether the claimed primers differ structurally from the corresponding naturally occurring DNA molecule because they have a 3-prime end.

Even taking all of the evidence as true and considering it in the light most favorable to Roche, however, no reasonable juror could conclude that there is a structural difference between the claimed primers and the corresponding naturally occurring segment of the *rpoB* gene to make the primers patentable under Myriad and In Re BRCA1-. It is undisputed that: (1) the complete MTB DNA molecule in its natural state is circular and has no ends; (2) the terms 3-prime and 5-prime may be viewed as a convenient way to distinguish one end of a DNA segment from the other (see Marconi Decl. ¶¶ 20, 32, Fig. 7; Gottesman Decl. ¶ 24); (3) the *rpoB* gene contained within MTB in its natural state as contained within the larger MTB DNA has no physical ends, though when viewed in isolation the relevant segment of DNA (i.e., the "signature nucleotides"

discovered by the inventors) could be seen as having ends, one of which could be identified as a 3-prime end; and (4) the claimed primers necessarily have 3-prime ends. The relevant question is whether the proper comparator to the claimed primers, for purposes of determining whether both have a 3-prime end, is the MTB DNA molecule as a whole (which is indisputably circular and has no ends in nature), or the relevant segment of the MTB DNA -- i.e., the signature nucleotides within the *rpoB* gene that are associated with MTB and rifampim-resistant MTB -- when examined in isolation.

In Re BRCA1-, the Federal Circuit stated: "Primers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind. They are structurally identical to the *ends of DNA strands* found in nature." 774 F.3d at 761 (emphasis added). The parties dispute what the Federal Circuit meant by "ends of DNA strands;" Roche contends that it intended to refer to the physical "end" of the entire DNA strand, millions of nucleotides away from the relevant segment of the DNA at issue, while Cepheid contends that the Federal Circuit was referring to the "end" of the relevant segment of DNA. While the opinion referred to "ends of DNA strands," the Federal Circuit implicitly rejected the notion of patentability of primers with identical sequences and a similar function to that found in nature, which is what is really at issue here. Significantly, the preceding sentence of the opinion states that, "Primers necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind." Thus, the Federal Circuit was focused on the particular sequence of the relevant segment of the DNA intended to be amplified, not on the far end of the DNA molecule millions of nucleotides away from that sequence. Likewise, while complete human and bacterial DNA take different forms -- one linear and one circular -- the primer claims at issue here relate only to short segments of DNA having 14-50 nucleotides, rather than the entire MTB chromosome (which has thousands of genes and millions of nucleotides). See Puknys Reply Decl. Ex. A (Gottesman Depo.) at 77-79; Gottesman Decl. Ex. 6 at 11. Dr. Gottesman testified that whether a chromosome is linear or circular makes no difference in designing a primer. Gottesman Depo. at 85-86.

Moreover, if the Court were to adopt Roche's position and distinguish the primers here

simply because they relate to circular bacterial DNA, rather than linear human DNA like that in In Re BRCA1-, the result would be a significant exception to the general unpatentability of primers for bacterial DNA as opposed to plant and animal (including human) DNA -- one that the Federal Circuit does not appear to have contemplated through a single reference to "ends of DNA strands" in the context of a much larger discussion of primer patentability. There is nothing in Myriad or In Re BRCA1- to suggest that the Federal Circuit meant to create such a distinction in the patentability of primers directed to related types of natural phenomena. Nor does there appear to be any rational purpose for such a distinction, which would create a more favorable playing field with respect to invention regarding bacterial DNA over human DNA.

Roche contends that Myriad itself reflects a human versus bacterial DNA distinction because it distinguishes between the patentability of DNA and cDNA. It is true that Myriad held that isolating naturally occurring DNA segments was not patentable, whereas the creation of a cDNA sequence was, because the latter results in "something new": a molecule that is not naturally occurring because the non-coding regions have been removed. However, the Court was drawing a distinction between naturally occurring and non-naturally occurring DNA. Roche also noted Myriad's reference to Diamond v. Chakrabarty, 447 U.S. 303, 309-10 (1980). Chakrabarty held that an invention which added four plasmids to a bacterium, enabling it to break down components of crude oil, was patentable as a "nonnaturally occurring manufacture or composition of matter - a product of human ingenuity 'having a distinctive name, character [and] use.'" Id. Myriad distinguished the modified bacterium in Chakrabarty, which had "markedly different characteristics from anything found in nature" due to the additional plasmids and ability to degrade oil, from the invention claimed in Myriad, which did not "create anything" but simply separated a gene from its surrounding genetic material. However, the distinction that Myriad drew was not based on whether the DNA at issue was human or bacterial; it was focused on whether something brand new was created. Myriad's reference to Chakrabarty reinforces this conclusion.

The proper comparator is the relevant corresponding segment of *rpoB* gene of the MTB DNA, which can be seen as having a 3-prime end when viewed as a smaller part of the whole DNA, and is therefore structurally identical to the claimed primers. Roche's position would

improperly conflate the entire MTB chromosome with the claimed short segments of the MTB *rpoB* gene at issue here. See Gottesman Depo. at 87 (distinguishing the gene which has ends from the circular chromosome containing the gene which does not). When examined in this way, there is no relevant structural difference between the claimed primers and the naturally occurring segment of DNA with respect to the 3-prime end.

b. 3-Prime Hydroxyl

According to Roche, another structural distinction is that the claimed primers are linked by hydroxyl groups, whereas naturally occurring DNA nucleotides are lined by phosphodiester bonds. Gottesman Decl. ¶ 26. Thus, Roche argues that the primers are chemically distinct from any DNA that occurs naturally and are analogous to the cDNA found patentable in Myriad. Gottesman Decl. ¶ 83; see also Marconi Decl. ¶ 29 (all primers must have a 3-prime hydroxyl group at the end to allow nucleotides to be added); Gottesman Decl. ¶ 48 (if a DNA does not have a free hydroxyl at the 3-prime end, it cannot be a primer). Dr. Gottesman's testimony is that MTB DNA in its natural, complete circular form does not have a 3-prime hydroxyl group at the end. See Gottesman Decl. ¶¶ 55, 84-86, Fig. 10; Gottesman Depo. at 79-80. According to Roche, this creates a triable issue of fact because, while the claimed primers in In Re BRCA1- were structurally identical to the corresponding human DNA strands found in nature, in contrast here the claimed primers have a 3-prime hydroxyl group at the end while naturally occurring MTB DNA does not.

Cepheid persuasively counters that Roche's argument that its primers differ from naturally occurring DNA because they have a 3-prime hydroxyl group fails when this case is compared to In Re BRCA1-. It is undisputed that neither naturally occurring BRCA1 nor *rpoB* sequences have 3-prime hydroxyl groups (see Gottesman Depo. at 83-84). In In Re BRCA1-, the Federal Circuit compared the primer to the relevant segment of naturally occurring DNA, which was taken from the middle and not the far end of the DNA molecule (as is also the case here), and did not find a meaningful distinction between the DNA segment and the claimed primer despite the fact that primer had a 3-prime hydroxyl group. Because that was insufficient to distinguish the primer in In Re BRCA1-, it is likewise insufficient here. Indeed, Roche's argument relating to this distinction

was raised in an opening brief before the Federal Circuit in In re BRCA1-. See In re BRCA1, Nos. 14-1361, -1366, 2014 U.S. Fed. Cir. Briefs LEXIS 400, **11-12, 65-66 (Fed. Cir. April 18, 2014). While the Federal Circuit did not expressly address the hydroxyl group argument in its opinion, it ultimately held that the primers were unpatentable and thus implicitly rejected it. Roche's argument is also unpersuasive for the same reasons stated above with respect to Roche's attempt to create a distinction based on the absence of a 3-prime end of the complete, circular bacterial MTB molecule.

For all of the foregoing reasons, the primer claims in this case, which have genetic sequences identical to those found in nature, are indistinguishable from those held to be directed to nonpatentable subject matter in In Re BRCA1-, and are not like the cDNA found to be patentable in Myriad. Summary judgment as to the primer claims is granted.

2. Patentability of Method Claims 1-13

Cepheid argues that method claims 1-13 are directed to methods of detecting MTB based on naturally occurring signature nucleotide sequences that have been amplified using conventional PCR techniques and are therefore unpatentable under Mayo. As explained above, in Mayo the Supreme Court set forth a two-step process for distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those claiming applications of those concepts that add enough to render them patent eligible. The first step is to determine whether the claims at issue are directed to a patent ineligible law of nature, natural phenomenon, or abstract idea. Mayo, 132 S. Ct. at 1297. If they are, the analysis proceeds to step two: the search for an "inventive concept" by considering the elements of each claim both individually and "as an ordered combination" to determine whether the additional elements "transform the nature of the claim'' into a patent eligible application. Id. at 1298.

In Mayo, the Supreme Court evaluated whether claims directed to methods for measuring metabolites in the bloodstream to determine appropriate drug dosages were patent eligible. At step one, the Court held that the claims attempted to patent an ineligible "law of nature" (how the drug compounds are metabolized by the body) despite the need for a human to administer the drug to trigger a reaction. 132 S.Ct. at 1296. The Court proceeded to step two, and evaluated whether

"the patent claims add *enough* to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that *apply* natural laws." Id. at 1297 (emphasis in original). The Court held that the claimed methods did not do so, because they required only well-known, routine activities previously used by scientists in the field and "appending conventional steps, specified at a high level of generality" was insufficient. Id. at 1297-1300.

a. Mayo Step One

The first question is whether the claims at issue are directed to a patent ineligible law of nature, natural phenomenon, or abstract idea. Mayo, 132 S. Ct. at 1297. Cepheid argues that the method claims here are based on the unpatentable discovery that the presence of position-specific signature nucleotides of a naturally occurring MTB *rpoB* gene indicates the presence of MTB. See '723 Patent at 2:60-3:2; 3:16-21; 3:37-39; see also Puknys Decl. Ex. A at 17 (inventors discovered that these "position-specific nucleotides serve as highly specific identifiers of M. tuberculosis" and "utilized this information as the basis" of the method of claim 1 for determining the presence or absence of MTB). Cepheid contends that the claimed discovery here -- the correlation between signature nucleotides and the presence of MTB -- is the same kind of discovery deemed an unpatentable law of nature in Mayo at step one.

Cepheid relies on Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015), cert. denied, 2016 WL 1117246 (U.S. June 27, 2016), which addressed the patentability of claims relating to a method for detecting paternally inherited cffDNA in maternal plasma to determine fetal characteristics using known laboratory techniques, which created an alternative to the prior, more risky methods of prenatal diagnosis of fetal DNA. Id. at 1373. The Federal Circuit held that the claims were directed to a "multistep method that starts with cffDNA taken from a sample of maternal plasma or serum - a naturally occurring non-cellular fetal DNA that circulates freely in the blood stream of pregnant women" and "ends with paternally inherited cffDNA, which is also a natural phenomenon." Id. at 1376. Accordingly, the Federal Circuit held that the method claims were directed to naturally occurring phenomena at step one of the Mayo analysis, and proceeded to step two.

Cepheid also relies on Genetic Tech. Ltd. v. Merial LLC, 818 F.3d 1369 (Fed. Cir. 2016),

which recently examined a method claim relating to amplification of non-coding regions of DNA to detect coding regions of DNA using primers, followed by analysis of the amplification product. Though the invention was useful to diagnose and treat genetic disorders and diseases, the Federal Circuit held that it was directed to a law of nature, i.e., the link between coding and non-coding regions of DNA. Id. at 1375-76. The Federal Circuit concluded that the use of primers in the amplification step did not alter its conclusion that the claim was directed to a law of nature because the primers' "sole function" was to amplify a naturally occurring DNA sequence. Id.at 1376. Cepheid argues that as in Ariosa and Genetic Tech. Ltd., at step one of the Mayo analysis the method claims here are directed to the discovery of a patent-ineligible naturally occurring phenomenon -- the correlation between the signature nucleotides and the presence of MTB. See Puknys Decl. Ex. 16.

Roche counters that the claimed methods of the patent are not directed to a naturally occurring phenomenon, because in May 1994 it was "not routine or conventional to use PCR (or any other genetic test) to detect the presence of MTB in a biological sample" and "unprecedented to perform PCR using the type of primer specified in claims 1 through 13." Opp. at 17. According to Roche, its claimed "new and improved" process is patentable because the discovery of position-specific signature nucleotides that distinguish MTB from other bacteria enabled the inventors to develop "an improved assay that for the first time enabled clinicians to diagnose the presence of MTB in a biological sample and to identify whether the MTB infection was likely to respond to rifampin." Id.

Roche focuses on the Federal Circuit's recent decision in Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042 (Fed. Cir. July 5, 2016). In CellzDirect, the Federal Circuit vacated a lower court's decision that the claims at issue were directed to a patent ineligible law of nature. At step one of the Mayo analysis, the Federal Circuit held that, though the claims were based on the discovery of a natural phenomenon (the ability of certain liver cells, or hepatocytes', to survive multiple freeze cycles), they were "directed to a new and useful laboratory technique for preserving hepatocytes. This type of constructive process, carried out by an artisan to achieve 'a new and useful end,' is precisely the type of claim that is eligible for patenting. . . . They

employed their natural discovery to create a new and improved way of preserving hepatocyte cells for later use." Id. at 1048 (quoting Alice, 134 S.Ct. at 2354).

Roche argues that its patented invention mirrors the one claimed in CellzDirect because the inventors discovered the natural phenomenon that certain signature nucleotides exist in a particular MTB gene, and then used this discovery to develop a new and improved process for detecting MTB and rifampin-resistant MTB that had significant advantages over prior art. See Gottesman Decl. ¶¶ 59, 77, 82. Roche contends that, following the reasoning of CellzDirect, at step one there is a triable issue of fact that method claims 1-13 are a "new and improved technique, for producing a tangible and useful result" distinguishable from inventions directed to patent-ineligible concepts.

Specifically, while Roche acknowledges that the background techniques of PCR amplification and detection were "routine" when the patent application was filed in 1994, it argues that it was not routine or conventional to use a genetic test to detect MTB or rifampin-resistance in a biological sample in 1994. See Gottesman Decl. ¶¶ 3-4, 54, 78; but see Gottesman Depo. at 53-74 (discussing prior art showing that PCR had been used to detect MTB by 1994). Roche also argues that it was also not routine or conventional to perform PCR using the particular primers specified in the method claims in 1994, as the first nucleic acid test for MTB was not approved by the FDA until 1996. See Gottesman Decl. ¶¶ 3, 54, 81-82. Thus, according to Roche, the invention which provided an improved PCR assay was a great advance in MTB diagnostics. Gottesman Decl. ¶¶ 4, 81-82; see also Rabinowitz Decl. Ex. 5 (Cepheid's website touting "revolutionary" benefits of its accused test that can simultaneously detect MTB and rifampin-resistance); Exs. 6-7 (Cepheid documents claiming benefits of accused test).

Roche's arguments relating to the benefits of the discovery are misplaced because scientific advance alone does not satisfy step one. While it may have been "surprising" to find signature nucleotides in MTB (see Gottesman Depo. at 82), the fact that a discovery of a natural phenomenon is unexpected does not make it patentable. The undisputed fact is that the inventors discovered that the *rpoB* gene of MTB has signature nucleotides (a "law of nature"), and then simply applied that discovery using the well-known technique of PCR to amplify and detect the presence of MTB and rifampin-resistant MTB without creating "something more." This is

comparable to the discoveries deemed non-patentable in Mayo, Ariosa, and Genetic Technologies. See Mayo, 132 S. Ct. at 1295-97 (discovery of natural correlation between level of certain metabolites and drug dosage, resulting in claimed method of optimizing treatment using standard techniques to administer the drug and then check if the metabolite level indicated a dosage change); Ariosa, 788 F.3d at 1373 (discovery of law of nature that pregnant women's blood contains cffDNA, resulting in claimed methods using standard techniques to amplify and detect cffDNA in maternal blood); Genetic Technologies, 818 F.3d at 1374 (discovery of natural correlation between non-coding regions of DNA and the presence of an allele in the coding region, resulting in claimed method of detecting alleles using standard PCR to amplify and detect).

In contrast, in CellzDirect, the inventors discovered a natural phenomenon (that some hepocytes could survive multiple freeze/thaw cycles), but then developed a "new and useful laboratory technique" for producing a desired preparation of the cells that involved several physical steps that provided a better way of producing that preparation of cells -- namely, freezing and thawing hepocytes twice even though the prior art taught away from this process. 827 F.3d at 1046-51 (distinguishing cases that did not invent a new and useful method based on the discovery of a natural phenomenon). Thus, the invention in CellzDirect went beyond applying a known lab technique to a newly-discovered natural phenomenon, and instead created an entirely new lab technique. No analogous new product or lab technique is claimed in the '723 Patent to take the method claims of the '723 Patent out of the realm of nonpatentable laws of nature or natural phenomena at step one.

b. Mayo Step Two

If the claims are directed to a patent ineligible law of nature or natural phenomenon, as here, the Court proceeds to step two and considers the elements of the claims both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim'' into a patent eligible application. Mayo, 132 S. Ct. at 1298. Cepheid argues that the method claims of the '723 Patent fail step two of the Mayo test because there is no "inventive concept" beyond the discovery of an unpatentable natural phenomenon (the correlation between signature nucleotides and the presence of MTB), coupled with a well-known scientific process

(PCR). Cepheid contends that the method claims contain two routine steps -- *amplification* of a portion of the *rpoB* gene of MTB, and then *detection* of the presence or absence of amplification product (which in turn indicates the presence or absence of MTB) -- using the PCR technique that was well known by 1994. See '723 Patent at 25:57-27:51; Marconi Decl. ¶¶ 24-25, 35, 49-56, Ex. 4; Gottesman Decl. ¶ 42; Gottesman Depo. at 190-92; 53-74 (acknowledging pre-1994 PCR-based MTB detection methods performed in lab without FDA approval). Whether viewed in isolation or in combination, according to Cepheid these steps do not show an inventive concept necessary to transform the method claims into a patent-eligible invention.

It is undisputed that the method claims are not directed to any change to the previously-known PCR process itself. See '723 Patent at 3:65-66 (invention uses "standard" PCR techniques); Gottesman Depo. at 131-133 (the improvement was "applying PCR to amplifying this region of the *rpoB* gene"). While Roche claims that it improved the technique of PCR as it was used to detect MTB by developing the claimed primers, the underlying PCR laboratory process was admittedly well-known and routinely used by 1994, and there is no argument that the inventors somehow modified or improved the underlying PCR technique itself. See id. at 53-74, 131-33; but see Gottesman Depo. at 162-64 (acknowledging that some laboratory experiments relating to PCR for detecting MTB occurred before 1994, but also testifying that these tests were not routine or conventional, even in laboratories). Moreover, when questioned about pre-1994 prior art, Roche's expert Dr. Gottesman acknowledged that a prior art reference identified natural mutations of nucleotides in the *rpoB* gene of MTB associated with rifampin resistance (i.e., the signature nucleotides claimed here), explained how to amplify this portion of the gene using PCR, and how to detect rifampin resistance -- all of which could lead one skilled in the art to detect MTB by performing a simple sequence comparison with other bacteria (such as the comparison claimed in the '723 Patent). See Gottesman Depo. at 32-33, 101, 104, 199; but see Gottesman Depo. at 105 (nothing in prior art reference predicts that there would be signature sequences in the rpoB gene); see also Marconi Decl. ¶¶ 52-56. As discussed further below, the fact that the PCR technique itself was well-known and routine distinguishes this case from CellzDirect, where a brand new laboratory technique was developed based on the underlying discovery of a

nonpatentable natural phenomenon and claimed as part of the method claims at issue there. Any factual dispute as to how routine it was to use PCR to detect MTB and rifampin-resistant MTB, whether in a lab or a clinic, is immaterial because the PCR test itself remained unchanged.

At step two, Cepheid relies on Genetic Technologies, where the Federal Circuit stated that both the claimed "amplifying" and "analyzing to detect" steps of PCR were well known by the time of the patent application. 818 F.3d at 1377. Genetic Technologies found that the technique of PCR was well known as early as 1989 for DNA amplification. Id. at 1377; see also Marconi Decl. ¶¶ 24-25; '723 Patent at 3:64-4:1 (acknowledging "increasing use [of PCR] in genotypic detection of drug resistance"). Cepheid argues that the claimed amplification and detection steps claimed here are similarly insufficient, individually and collectively, to provide an inventive concept. Specifically, according to Cepheid, the amplification step of PCR cannot be the "inventive concept" in the '723 Patent because it was well known at the time of the patent application. See Gottesman Depo. at 21-24, 28-31, 137-38. Likewise, the preparation of the primers identified in the '723 Patent was based on well-known techniques, and their sole function is to amplify naturally occurring DNA. See '723 Patent at 25:61-63, 5:53-63, 6:11-16; Gottesman Depo. at 23. Further, the "detecting" step (detecting the presence or absence of amplification product using gel electophoresis) was also well known by 1994. See Marconi Decl. ¶¶ 34-35, 50; '723 Patent at 14:42-48; Gottesman Depo. at 21-24, 101, 137-38. Finally, the comparative mental step of detecting the presence or absence of amplification product to determine the presence or absence of MTB is similar to the mental steps in Mayo, Ariosa and Genetic Technologies that did not render the claims patentable at step 2. Cepheid argues that dependent claims 2 through 13, individually and collectively, fail to add anything inventive to unpatentable method claim 1.

Roche counters that CellzDirect supports its position at the step two analysis. Because the Federal Circuit found that the claims survived Mayo step one, it did not need to proceed to step two. However, the Federal Circuit explained that even if it proceeded to step two, the patent at issue "recites an improved process for preserving hepatocytes for later use. The benefits of the improved process over the prior art methods are significant." Id. at 1050. While the individual steps of freezing, thawing and separating were well known, the claimed process of freezing and

thawing *twice* was "far from routine and conventional" when viewed as an ordered combination of elements; instead, the prior art taught away from this process. Id. at 1051. Roche argues that its claimed method of amplifying "specific, identified signature nucleotides" similarly satisfies step two as an improved process for detecting MTB and rifampin-resistant TB that provides significant benefits over prior art.

However, what made the CellzDirect invention patentable was not merely the fact that it was an "improvement" or provided "significant benefits," but the fact that it was a brand new process that not only had not been done before, but indeed had been commonly understood as unworkable. Here, while the primers used and the discovery that these primers would bind to naturally-occurring signature nucleotides indicative of the presence of MTB and rifampin-resistant MTB were new discoveries, they are non-patentable natural phenomena for the reasons discussed above. The use of newly developed, non-patentable primers to bind to newly identified naturally occurring signature nucleotides (not patentable under Myriad) using the well-known, routine process of PCR in a conventional way does not transform the claimed methods into "something more." See Ariosa, 788 F.3d at 1377 (applying new discovery of natural phenomenon that paternal DNA could be detected in mother's blood to standard PCR process for the first time did not make claims patent-eligible).

Roche also attempts to distinguish its invention from the unpatentable method claims in In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litig., 774 F.3d 755 (Fed. Cir. 2014). In In re BRCA1-, the Federal Circuit declined to decide whether the method claims failed as unpatentable claims that simply identified a law of nature and applied conventional techniques, holding that the method claims were unpatentable because they recited abstract ideas. Id. at 762. The Federal Circuit had previously determined in a separate opinion that the first method step -- the "comparison" step of comparing two nucleotide sequences and determining similarities and differences -- claimed a patent-ineligible abstract mental process. Id. at 763 (citing Myriad, 689 F.3d at 1334). The Federal Circuit noted that the "number of covered comparisons is unlimited," "not restricted by the purpose of the comparison or the alteration being detected," and "covers detection of yet-undiscovered alterations, as well as comparisons for purposes other than detection

of cancer." Id. at 763-64. It thus concluded that "allowing a patent on the comparison step could impede a great swath of research relating to the BRCA genes, and it is antithetical to the patent laws to allow these basic building blocks of scientific research to be monopolized." Id. at 764.

The Federal Circuit proceeded to Mayo step two, and evaluated whether the "particular mechanism for the comparisons added by claims 7 or 8 renders the claims patent-eligible." Id. at 764. The comparison at issue involved: for claim 7, "1) hybridizing a BRCA gene probe and 2) detecting the presence of a hybridization product. Similarly, claim 8 requires 1) amplification of the BRCA1 gene and 2) sequencing of the amplified nucleic acids." Id. The Federal Circuit held that these additional elements were "well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent applications" and "do nothing more than spell out what practitioners already knew -- how to compare gene sequences using routine, ordinary techniques. Nothing is added by identifying the techniques to be used in making the comparison because those comparison techniques were the well-understood, routine, and conventional techniques that a scientist would have thought of when instructed to compare two gene sequences." Id. In Re BRCA1-'s analysis of the steps of the method claims before it applies equally to the routine and well-known method steps of PCR amplification and detection claimed here. The fact that newly developed primers were used does not change the analysis.

In re BRCA1- distinguished the unpatentable method claims 7 and 8 discussed above from the potential patentability of a different method claim, claim 21, that was not then before the Federal Circuit, pointing out that the arguably patentable method claim 21:

> claims a method of detecting alterations in which the alterations being detected are expressly identified in the specification by tables 11 and 12.5. These tables expressly identify ten predisposing mutations of the BRCA1 gene sequence discovered by the patentees. Thus, the detection in claim 21 is limited to the particular mutations the inventors discovered: detecting ten specific mutations from the wild-type, identified as "[p]redisposing [m]utations," for the specific purpose of identifying increased susceptibility to specific cancers. Claims 7 and 8 are significantly broader and more abstract, as they claim all comparisons between the patient's BRCA genes and the wild-type BRCA genes.

In re BRCA1-, 774 F.3d at 765 (internal citations omitted). Roche argues that its method claims

are analogous to claim 21 and distinguishable from claims 7 and 8 in In re BRCA1-, because they require amplification of one of eleven signature nucleotides, expressly identified in the claims, and are thus restricted by the purpose of the detection and the specific nucleotide sequences. See '723 Patent at 26:58-68. However, the Federal Circuit's discussion of claim 21 was dicta, and the Federal Circuit "express[ed] no view" on whether claim 21 was patentable. In re BRCA1-, 774 F.3d at 765. Further, the Federal Circuit was considering the issue of "abstract ideas" rather than "natural phenomenon." There appears to be a distinction between narrowing an unpatentable abstract idea into something more specific (and thus no longer abstract and instead potentially patentable), as opposed to narrowing a broadly claimed natural phenomenon to a more specific natural phenomenon, each of which would be unpatentable. Finally, the Federal Circuit rejected similar reasoning in Ariosa, holding that claims focused on detecting a specific chromosome within cffDNA added no inventive concept to the limitations of the claim. 788 F.3d at 1379. Thus, Roche's reliance on this portion of In re BRCA1- is unpersuasive.

Roche also attempts to distinguish Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1376 (Fed. Cir. 2016). There, at step two of the Mayo analysis, the Federal Circuit held that the claim at issue did not sufficiently add an inventive concept because the step of amplifying DNA with a primer pair through PCR was well-established at the time of the patent application, and the other step of analyzing the amplified DNA was also well known in the field at the time. Id. at 1377. Thus, whether considered separately or in combination, the steps did not "provide sufficient inventive concept to render [the claim] patent eligible." Id. The Federal Circuit relied on Mayo, Ariosa, and In Re BRCA1- to reject an argument that the "detection" step supplied an inventive concept, holding that it was an unpatentable "routine comparison that can be performed by the human mind." Id. at 1378. Roche argues that in Genetic Techs. Ltd., the method claims were not limited to detecting the specifically identified nucleotides that the inventors discovered (as is the case here, where the claims are limited to eleven specific nucleotides), but broadly covered all applications of the underlying natural phenomenon. Id. at 1375.

Similarly, Roche attempts to distinguish Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1375, 1381 (Fed. Cir. 2015), cert. denied, No. 15-1182, 2016 WL 1117246 (U.S. June

27, 2016). In Ariosa, the Federal Circuit rejected the patent holder's argument that the invention included patent eligible applications of a naturally occurring phenomenon, because the method claimed amounted to "a general instruction to doctors to apply routine, conventional techniques [including PCR] when seeking to detect cffDNA." Id. at 1377. Thus, despite an acknowledgement that the invention was a "positive and valuable contribution to science" that "revolutionized prenatal care," the Federal Circuit found that the claims were not directed to patentable subject matter. Id. at 1379-80. As above, Roche argues that this case is distinguishable because the claims at issue were not limited to detecting or analyzing any particular nucleotide sequences, whereas here the claimed methods use primers that bind to eleven specific signature nucleotides and require "specific amplification steps that were not routine or conventional in 1994 to detect MTB." Opp. at 22 (citing Gottesman ¶ 3, 81-82).

However, Roche's attempts to distinguish Genetic Technologies and Ariosa are unpersuasive because the identification of specific naturally-occurring nucleotides or the use of primers developed based on this identification simply does not confer patentability where there is no new, inventive concept added to the well-known underlying method so as to satisfy the step two analysis. This is true even where the invention, when viewed as a whole, could be seen as "revolutionary." See Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371, 1380–81 (Fed. Cir. 2015), cert. denied, 136 S. Ct. 2511, 195 L. Ed. 2d 841 (2016) (Linn, J., concurring) (concurring that claims were unpatentable under the "sweeping language of the test set out in Mayo," but articulating a belief that, where the amplification and detection of cffDNA had never before been done, "[t]he new use of the previously discarded maternal plasma to achieve such an advantageous result is deserving of patent protection" and finding "no reason, in policy or statute, why this breakthrough invention should be deemed patent ineligible." Summary judgment as to the method claims is also warranted.

V. CONCLUSION

For all of the foregoing reasons, Cepheid's Motion for Summary Judgment is GRANTED.

IT IS SO ORDERED.

Dated: January 17, 2017

ELIZABETH D. LAPORTE
United States Magistrate Judge